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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicant: Schally, et al.
Serial No.: 727,105 Group Art Unit: 153
Filed: 4/25/85 Examiner: D. Phillips
FOR: BIOLOGICALLY ACTIVE OCTAPEPTIDES

Edison, N.J. 08837

#6
7/25/86

DECLARATION UNDER RULE 37 CFR 1.132

ANDREW V. SCHALLY declares and says that:

1. He is the Andrew V. Schally who is one of the co-inventors in the present application.

2. He has read the outstanding Official Action and that references cited therein.

3. He attaches hereto and makes a part hereof as Exahibit A, a publication by Wilfred Bauer, et al., published in Life Sciences, 31, 1133-1140 (1982).

4. Table 1 of the aforesaid Bauer article shows the growth hormone (GH) inhibition potencies in vivo for a number of compounds which Bauer prepared. The best of these compounds is SMS 201-995, an octapeptide containing a cysteine bridge having a D-Phe moiety at one end and a Thr (ol) moiety at the other end of the central hexapeptide core. In view of the substantial superiority of this compound over the other Bauer compounds, the comparative discussion relating to the relationship of Bauer's compounds and Applicants compounds will be restricted to the SMS 201-995 compound.

5. As will be seen from Table 1, in vivo potency superiority of SMS 201-995 over somatostatin (SRIF) is a factor 70.

6. A consideration of Applicants specification at page 12, Table C, indicates that Applicants compounds RC121-2H, RC121, and RC160 have an activity in a similar test as that of pagragraph 4 above of 118, 199, and 134 respectively, thus indicating a level of activity of approximately 1-1/2 to 3 times that of the best Bauer compound. The latter 2 compounds being of the order of about 2 to 2.75 times as active as SMS 201-995.

7. Attention is further drawn to Table 2 of the Bauer paper and Figure I of the enclosed PNAS USA 83 (1986) 1896 paper, which is attached hereto and made a part hereof as Exhibit B. (It should be noted that while Table 3 of the PNAS paper is substantially comparable to the Table C of the present application, the Table C figures are more recent and accurate).

8. In Figure 1 of the attached PNAS paper, the time course of serum GH levels is plotted for somatostatin RC121 and RC160. It will be noted that the curve for somatostatin (SS-14) shows minimum serum level 15 minutes after administration followed by an immediate rise in levels. By comparison, RC160 reaches its minimum level at 30 minutes and continues substantially unchanged for 120 minutes, while RC121 containues to suppress GH levels (below that of SS-14) up to 60 minutes after administration at similarly, the 15 minute level at 120 minutes. This demonostrates a far longer efficacy time than somatostatin.

By comparison, Bauer Table 2, shows an SRIF (same as SS-14) activity path analagous to that shown in the PNAS paper. The SMS 201-995 maintains its minimum levels to the 30 minute mark, but thereafter rises dramatically in

the following 30 minutes. It is therefore clear from a comparison of the PNAS Figure 1 with Bauer Table 2, that the time efficacy of Applicants compounds is at least twice as long as the best Bauer compound.

9. Since the compounds in question are intended to be used in pharmacological administration, the effective time of activity of a compound in a system is as important a consideration as the absolute level of efficacy when first administered.

Based upon the foregoing facts, it is my conclusion that with respect to GH activity, compounds RC121 and RC160 are <u>at least</u> between 4 and 6 times as effective as Bauer's SMS 201-995 compound.

10. As shown on Table 4 of the PNAS paper, Applicants have carried out experiments on the suppression of gastric acid secretion in dogs comparing said suppression obtained by the administration of a standard dose of SS-14 with the gastric acid suppression obtained by the administration of RC121 and RC160. These show that RC121 and RC160 are 4.75 and 4.33 times as effective as somatostatin. In a similar test utilizing the Bauer SMS 201-995 compound, the equivalent potency was 3.66.

Given the foregoing finding that the RC121 and RC160 compounds have an <u>in vivo</u> effective life of about 2 to 3 times that of 201-995, the actual dosage efficacy in gastric acid secretion of RC121 and RC160 is between 40 and 90% greater than SMS 201-995.

I hereby declare that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge

that willful or false statements so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

FURTHER DECLARANT SAYETH NOT.

Andrew V. Schally

ANDREW V. SCHALLY

DATE: JUNE 12, 1986

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